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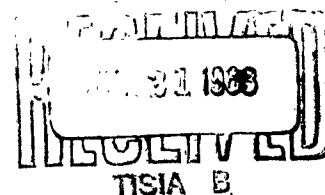
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**A CYTOGENETIC STUDY OF SOME RADIUM
DIAL-PAINTERS AND THEIR PROGENY**

TECHNICAL DOCUMENTARY REPORT NO. SAM-TDR-63-1

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**USAF School of Aerospace Medicine
Aerospace Medical Division (AFSC)
Brooks Air Force Base, Texas**



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FOREWORD

This report was prepared by the following personnel at the Graduate School of Public Health and the School of Medicine, University of Pittsburgh:

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ABSTRACT

Preliminary cytogenetic analyses were performed on four radium dial-painters and the crude average exposure dose to their bone marrow was estimated. Two instances of increased aneuploidy and three of increased chromosomal aberrations were observed in the four subjects, who had cumulative average bone marrow doses of 800 to 1,400 rem obtained at an average dose rate of 20 to 35 rem a year.

Cytogenetic analyses were also performed in the progeny of four dial-painters, selected because of a history of frequent miscarriages and congenital anomalies. Among these were three instances of definite congenital anomaly. Increased aneuploidy was observed in all three patients.

Additional observations and increased knowledge about the dosimetric and cytogenetic methods used are necessary before these preliminary findings can be adequately interpreted.

This technical documentary report has been reviewed and is approved.


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A CYTOGENETIC STUDY OF SOME RADIUM DIAL-PAINTERS AND THEIR PROGENY

1. INTRODUCTION

Improved cytogenetic methodology has made possible the recognition of chromosomal aberrations in dividing human blood and bone marrow cells after radiation exposure. Increased aneuploidy and morphologic abnormalities were reported by Tough et al. (1) in two radiation therapy cases; by Bender and Gooch (2) in eight workers involved in a nuclear criticality accident; in patients receiving therapeutic doses of I^{131} by Boyd et al. (3); and after diagnostic x-irradiation by Stewart and Sanderson (4). Association has been reported of chromosomal aberrations with various congenital anomalies (5), and with some forms of leukemia which are also increased in incidence following radiation exposure (6).

The ingestion of radium by women employed in painting watch dials with luminous paint in the early decades of this century has produced a human population group undergoing continuous internal radiation exposure. In the course of long-term surveillance of members of this group by Hasterlik, Finkel, and Miller at the Argonne Cancer Research Hospital and National Laboratory, an incidental observation has been that a number of their progeny exhibit various abnormalities which might stem from genetic transmission.

It was, therefore, considered of interest to determine, first, whether any cytogenetic abnormalities were present in the blood cells of persons exposed to long-term internal irradiation from radium; and, second, whether any cytogenetic evidence could be found for a possible relationship between a significant maternal body burden of radium and anomalies in the progeny. A pilot investigation was carried out on four dial-painters, the progeny of

two of them, and the progeny of two other dial-painters. A preliminary abstract concerning the cytogenetic findings in the dial-painters has appeared (7).

2. DIAL-PAINTER STUDIES

Medical history

Points of interest in the medical histories of the four dial-painters studied are listed in table I. The patients are arranged in descending order of magnitude of radium body burden. The numerical designation is from the International Register of Radium Dial-Painters.

Radiation exposure

The sole experimental observation available in attempting to determine radiation exposure in these patients is the measurement of the current radium body burden. This study has been carried out at Argonne National Laboratory by whole-body radiation counting and, in some cases, by breath radon determinations as well. The crude marrow dose estimate (table II) was based on many uncertain assumptions, which will be discussed below. There was insufficient factual information with which to attempt even a crude dose estimate for radiation exposure of the gonads in these patients.

TABLE I
Pertinent medical history of radium dial-painters

Patient No.	Medical history
03-402	Osteogenic sarcoma of femur
03-459	Osteogenic sarcoma of femur
03-417	Carcinoma of jaw
03-423	No relevant findings

TABLE II
Crude estimate of radiation dose to bone marrow of radium dial-painters

Patient No.	Radium body burden (μ c.)	Crude marrow dose estimate		
		Alpha* (rem)	Beta* (rem)	Total (rem)
03-402	1.19	1,340	90	1,430
03-459	1.16	1,150	77	1,227
03-417	0.76	860	58	918
03-423	0.60	770	51	821

* $RBE_{\alpha} = 10$; $RBE_{\beta} = 1$.

The alpha dose was based on the ICRP¹ calculations (8) of the average radium dose to bone and Spiers's calculations (9) of alpha doses to marrow adjacent to bone. Correction was made for the elimination of radium with time, using the ICRP-recommended power function: $A(t) = 0.54 t^{-0.52}$. An average non-uniformity concentration factor of 10 was employed, on the basic work of Hindmarsh et al. (10) and of Lloyd (11). The values for proportion of bone to bone marrow in spongy bone developed by Engstrom et al. (12) were used to estimate an upper limit to the alpha dose averaged over the total marrow mass. To convert alpha doses in rads to rems, an RBE of 10 was assumed.

¹International Commission on Radiological Protection.

For the beta dose, an average energy of 0.29 Mev per particle was used. The estimates of beta dose at the edge of marrow made by Hindmarsh et al. (10) for Sr^{90} were adjusted for the differences in average beta energies to obtain the beta dose at "hot spots" of high radium accumulation. A dose nonuniformity factor of 2.6 was obtained, and the average and maximum beta doses to the marrow and bone were estimated.

The gamma rays emitted are long range and their contribution was considered negligible compared with the absorbed energy of the alpha and beta particles in this crude estimate.

If the resultant rem doses are divided by the duration of exposure, almost forty years, about 20 to 30 rems a year is the estimated average dose rate to the bone marrow.

Cytogenetic findings

Heparinized venous blood samples were collected in Chicago and flown to Pittsburgh in refrigerated containers for cytogenetic processing within 8 hours after collection. The cytogenetic technique used was a peripheral blood cell culture method modified from the version of Osgood's gradient method described by Moorhead et al. (13). Approximately 35 cells have been counted and analyzed thus far in each case and about 10 of these have been karyotyped. The results are summarized in table III.

TABLE III
Cytogenetic findings in blood cells of radium dial-painters

Patient No.	Age (yr.)	Cells studied	Counts $\neq 46$	Chromosomal aberrations	Chromosome aberrations
				(Percent)	
03-402	57	38	21.1	2.6	2.6
03-459	55	33	12.1	6.1	0.0
03-423	54	31	12.9	6.5	3.2
03-417	53	37	27.0	2.7	13.5
14 normals	15-41	312	14.7	6.1	0.0

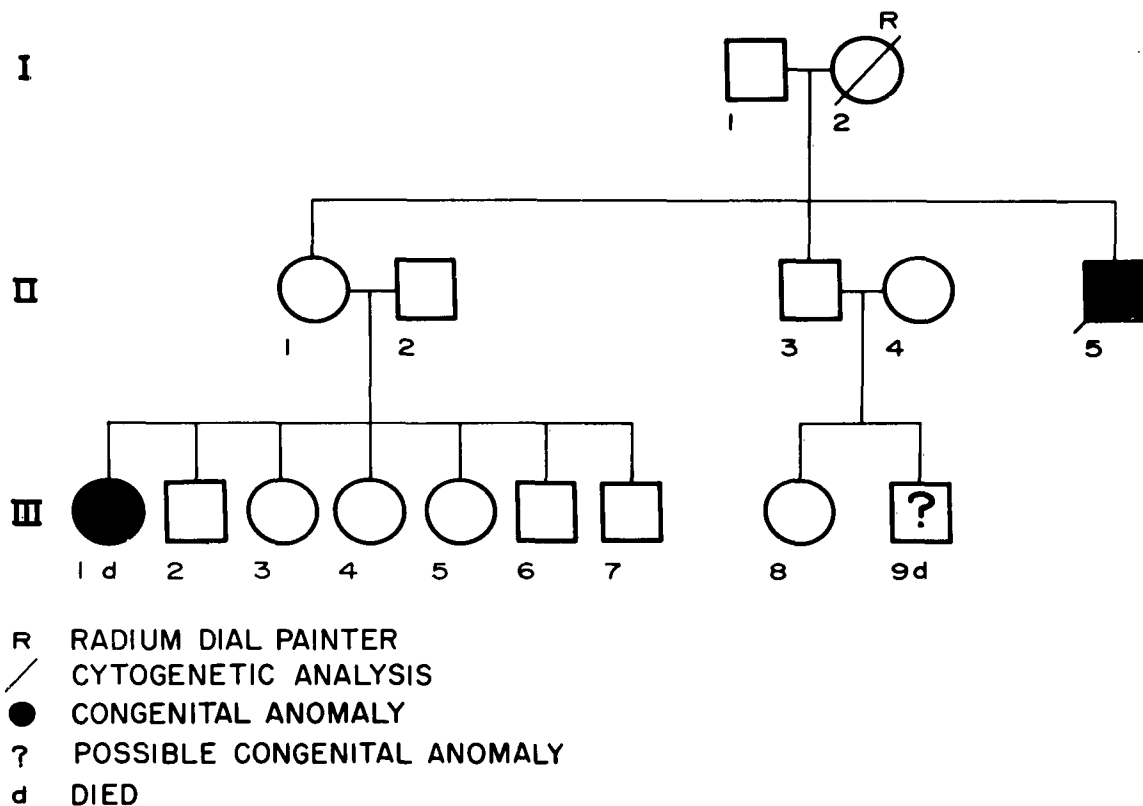


FIGURE 1

Pedigree of radium dial-painter No. 03-459.

Two of the dial-painters show greater aneuploidy than the fourteen normals. The latter group was accumulated at an earlier stage in our work, and continuing changes and improvements in technic probably would result in a lower amount of apparent aneuploidy secondary to cytogenetic methodology at this time. The comparison, therefore, is probably conservative.

The incidence of chromatid aberrations does not appear to be increased over that in the control group. However, the two patients with increased aneuploidy and one other show some chromosome aberrations. These are not present in the controls. They include isochromatid breaks and consistent achromatic areas on both chromatids of two analogous chromo-

somes. One apparent ring chromosome was seen, but no dicentrics were found.

3. DIAL-PAINTER FAMILY STUDIES

Pedigrees of families studied

The pedigrees of radium dial-painters 03-459, 03-423, 03-417, and 03-658 are presented in figures 1, 2, and 3. It will be noted that painters 03-423 and 03-417 are sisters and that their pedigrees are drawn on the same chart (fig. 2).

Medical history of progeny

The relevant history of the progeny of the radium dial-painters is presented in table IV.

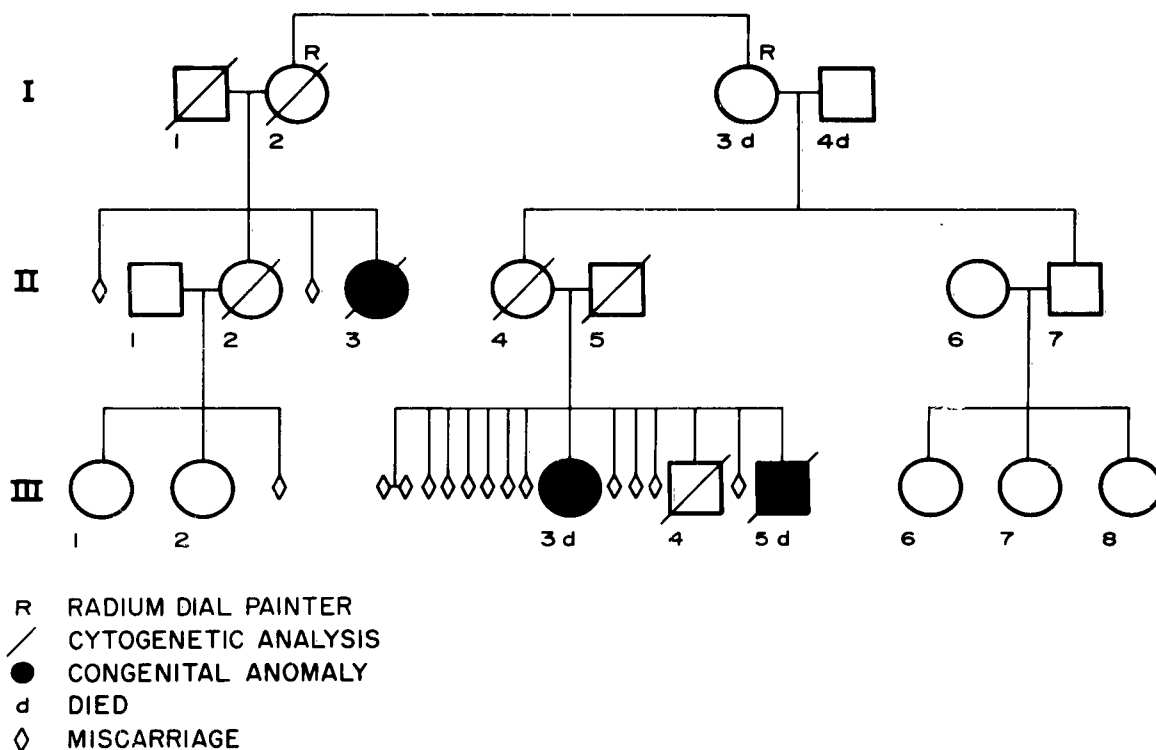


FIGURE 2

Pedigree of radium dial-painters Nos. 03-423 and 03-417.

The individuals are referred to in accordance with standard genetic nomenclature, which is keyed to their location on the pedigree drawings in figures 1, 2, and 3.

It is of note that the delivery of the cerebral palsy patient designated as II-5 in figure 1 was a complicated forceps procedure. While the cerebral palsy syndrome may be inherited, it also may be acquired *in utero*, at delivery, or later. The obstetrical history suggests that this instance should not be regarded as a definite congenital anomaly.

Another point of interest is that the mother of the mongoloid designated as II-3 in figure 2 was 37 years old at the time of the child's birth. Thus she is an older-aged mother, as are the majority of mothers of mongoloids.

Cytogenetic findings

Approximately 25 cells were examined and approximately 10 karyotyped in each case. The results are presented in table V.

It will be seen that in five instances aneuploidy exceeded that of the normal control group. Three of these were the patients in whom a definite congenital anomaly was diagnosed. In the equivocal instance of the patient with cerebral palsy, increased aneuploidy was not found.

A slight increase in aneuploidy was observed in the apparently normal husband of dial-painter 03-423, as well as some increase in chromatid aberrations. A greater percentage of aneuploidy was found in the apparently normal husband of one of the progeny.

The morphologic abnormalities of the chromatids were similar to those found in the dial-painters themselves—that is, breaks and achromatic regions. The chromosomal abnormality in one cell of the mongoloid patient was a smaller-than-normal G group chromosome, similar in appearance to the Ph 1 chromosome of Nowell and Hungerford (18). Hematologic study of peripheral blood and bone marrow in this case revealed no evidence of leukemia.

4. DISCUSSION

The results of this preliminary pilot study are clearly insufficient to provide definitive answers to the questions raised concerning the effect of radium deposited in bone on the bone marrow cells of the dial-painters and on the germ cells which resulted in their progeny. However, this initial examination of the question has shown an increase in aneuploidy in the peripheral blood cells of two of the dial-painters and in the three progeny with definite congenital anomalies that were studied. The

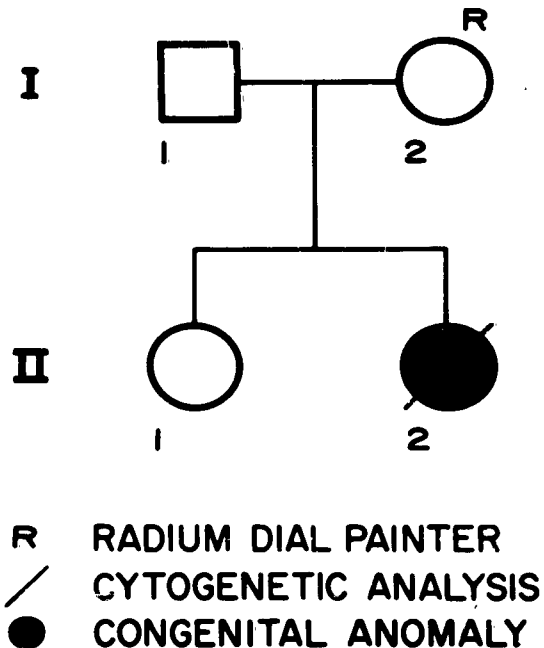


FIGURE 3

Pedigree of radium dial-painter No. 03-658.

TABLE IV

Medical history of abnormal progeny of radium dial-painters

Figure No.	Progeny of —	Pedigree designation	Medical history
1	03-459	II-5	Cerebral palsy with mental retardation.
		III-1	Omphalocele.
		III-9	Died one hour after birth, suggesting possible congenital anomaly.
2	03-423	II	Two miscarriages in third gestational month.
		II-3	Mongolism. Hearing defect.
		III	Miscarriage in third gestational month.
	03-417	II-7	Recurrent bacterial infections.
		III	Miscarriage of twins at fifth gestational month. Ten miscarriages at third to fourth gestational month.
3	03-658	III-7	Died three hours after birth. Congenital heart disease and coarctation of aorta.
		III-5	Died at three months. Multiple congenital anomalies.
		III-6	Recurrent bacterial infections.
		III-7	Recurrent bacterial infections.
		III-8	Recurrent bacterial infections.
3	03-658	II-2	Dwarfism.

TABLE V
Cytogenetic findings in blood cells of progeny of radium dial-painters

Figure No.	Family of —	Pedigree designation	Relation-ship	Age (yr.)	Congenital anomaly	Cells studied	Counts \neq 46	Chromatid aberrations	Chromosome aberrations
							(percent)		
1	03-459	II-5	P	21	\pm	25	4.0	8.0	0.0
		I-1	H	53	—	27	18.6	11.1	0.0
2	03-423	II-2	P	24	—	25	4.0	4.0	0.0
		II-3	P	16	+	34	20.6*	8.7	2.9†
		II-4	P	34	—	26	7.6	11.7	0.0
2	03-417	II-5	HP	35	—	25	32.0	8.0	0.0
		III-4	P	3	—	25	8.0	4.0	0.0
		III-5	P	$1/12$	+	25	20.0	4.0	0.0
3	03-658	II-2	P	27	+	25	20.0	8.0	0.0
14 normals				15-41		312	14.7	5.1	0.0

H, Husband of dial-painter; HP, husband of progeny; P, progeny of dial-painter.

*Counts \neq 47.

†Other than trisomy of a G group chromosome.

significance of these findings must await further analysis of these cases, as well as the study of more patients and their progeny.

One important question which deserves consideration in connection with the observations on the dial-painters themselves is whether the cells which divide in peripheral blood culture are of bone marrow descent. If they are produced in the lymph nodes, as recent work by MacKinney et al. (14) appears to suggest, this method may be an inappropriate way to study bone marrow radiation effects. This problem is currently being investigated by our group as well as by others.

If the dividing cells are accepted as descendants of bone marrow cells, it is still not a simple matter to arrive at a theoretic mechanism by which these findings were produced. The morphologic chromosomal abnormalities might be due to radiation effect, either on the cells examined or on their precursors at any time since the radium was first ingested, or both. They may be the result of one interaction or the cumulative result of several interactions with succeeding generations of cells over the

years. They may be the resultant of damage plus repair.

The incidence of abnormalities is also a function of both injury and repair mechanisms. In addition, other diverse stresses, such as aging of the subjects (15) and aerial transportation of the blood specimens, may have contributed to the findings reported herein, and the use of a more appropriate control group than was possible in this pilot study is indicated. It should be noted, however, that heparinization and refrigeration alone have not produced these changes in our laboratory.

Another difficult problem is the quantitative determination of the radiation exposure which may have produced the results observed. The dose to bone marrow cells was estimated only after making large and speculative simplifying assumptions. The computation of even a crudely estimated dose to the gonads was not possible because of the paucity of relevant information concerning the geometry of the exposure situation. Further investigations are clearly needed on this subject.

It must be borne in mind that the families studied in this preliminary investigation were selected because of the known history of abnormal progeny. There is no information at this time concerning the actual incidence of such abnormalities in the progeny of the total dial-painter population as compared to a suitable control group. Such a survey is planned to study this question more adequately.

No specific association of any of the various defects of the progeny with radiation exposure of the parent or grandparent is known from other studies. Although such an association was recently suggested for mongolism

(16), the presently available evidence (17) failed to support it.

The finding of one G group chromosome smaller than normal in the mongoloid patient is intriguing in view of three related observations. These are the presence of such a chromosome, the Ph 1 chromosome, in chronic granulocytic leukemia (18) and possibly in acute leukemia as well (19), the relationship between mongolism and leukemia (20), and the relationship between radiation and leukemia (6). Obviously, no definitive conclusions can be drawn on the basis of one abnormal chromosome in one cell, but this patient will be observed closely for future developments.

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<p>USAF School of Aerospace Medicine, Brooks AF Base, Tex.</p> <p>SAM-TDR-63-1. A CYTOGENETIC STUDY OF SOME RADIUM DIAL-PAINTERS AND THEIR PROGENY. Apr. 63, 7 pp. incl. illus., tables, 20 refs.</p> <p>Unclassified Report</p> <p>Preliminary cytogenetic analyses were performed on four radium dial-painters and the crude average exposure dose to their bone marrow was estimated. Two instances of increased aneuploidy and three of increased chromosomal aberrations were observed in the four subjects, who had cumulative average bone</p>	<p>1. Radiobiology</p> <p>2. Hematology, radiation</p> <p>3. Cytogenetics, radiation</p> <p>I. AFSC Task 775703</p> <p>II. Contract AF 41(657)-361</p> <p>III. University of Pittsburgh, Graduate School of Public Health, Pittsburgh, Pa.</p> <p>IV. N. Wald, C. E. Miller, W. H. Borges, et al.</p> <p>V. In ASTIA collection</p>	<p>USAF School of Aerospace Medicine, Brooks AF Base, Tex.</p> <p>SAM-TDR-63-1. A CYTOGENETIC STUDY OF SOME RADIUM DIAL-PAINTERS AND THEIR PROGENY. Apr. 63, 7 pp. incl. illus., tables, 20 refs.</p> <p>Unclassified Report</p> <p>Preliminary cytogenetic analyses were performed on four radium dial-painters and the crude average exposure dose to their bone marrow was estimated. Two instances of increased aneuploidy and three of increased chromosomal aberrations were observed in the four subjects, who had cumulative average bone</p>	<p>1. Radiobiology</p> <p>2. Hematology, radiation</p> <p>3. Cytogenetics, radiation</p> <p>I. AFSC Task 775703</p> <p>II. Contract AF 41(657)-361</p> <p>III. University of Pittsburgh, Graduate School of Public Health, Pittsburgh, Pa.</p> <p>IV. N. Wald, C. E. Miller, W. H. Borges, et al.</p> <p>V. In ASTIA collection</p>
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